PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification/ Update	1a/ 1b	A Systematic Review and Network Meta-Analysis of changes in average daily gain (ADG) and mortality associated with the use of commercially available Porcine Circovirus II (PCV-II) vaccines in swine naturally infected with PCV-II: An update
Registration	2	The protocol for the systematic review will be made available on the Systematic Reviews of Animals and Food (SYREAF – http://www.syreaf.org/protocol/) website.
Authors:		
Contact	3a	Annette O'Connor, Evidence and Epidemiology Consulting, Okemos Michigan Derald Holtkamp:
Contributions	3b	DH conceived the idea and provided guidance on eligibility. AOC provided guidance on the approach to review and analysis and report preparation
Amendments	4	Not applicable
Support:		
Sources	5a	Merck Animal Health
Sponsor	5b	Merck Animal Health
Role of sponsor or funder	5c	The sponsor will provide support for understand relevant studies and guidance about characteristics of studies that are important. This contract does not include publication.
INTRODUCTION		
Rationale	6	Since several products became commercially available in 2006, Porcine circovirus type II (PCV-II) vaccines have become one of the most intervention strategies in growing pigs. Many trials document the efficacy of PCV-II vaccines; however, head-to-head comparisons of vaccines are rarely conducted. The absence of this information leaves a gap in the evidence base. Network meta-analysis is a statistical tool that can estimate the comparative efficacy of multiple interventions even when direct comparisons are not available. In 2014, a network meta-analysis was

		published that compared the ADG associated with the use of commercially available PCV-II vaccines. Since the 2014 review, several relevant studies have been published such that it is important to update the meta-analysis to ensure producers and veterinarians have current comparison information.
Objectives	7	The objective of this review is to update the previously conducted review published in 2014. The reviewer question is "What is the effect of each of commercially available PCV2 vaccines used in piglets on the average daily gain and mortality from wean to finish in commercial pigs naturally exposed to PCV2 where the porcine reproductive porcine reproductive and respiratory syndrome virus (PRRSV) status is known?"
METHODS		
Eligibility criteria	8	The specific PICOD elements, which define the eligibility criteria, are as follows: • Population (P): Swine raised in intensive production systems with known PRRSV status • Intervention (I): The intervention (I) is defined a PCV-II vaccine. For vaccines, the product must be a commercially available PCV-II vaccine administered to piglets using the registered regime in the country of utilization/registration (dose, route, age of animal). We include previous formulations in the definition of commercially available vaccine, which will be treated as separate interventions. • Comparator: Placebo, or any commercial PCV-II vaccine. • Outcomes: The outcomes of interest are average daily gain and mortality from wean to finish. • Design: Controlled trial with random or systematic allocation of animals to the intervention in either group or individually and naturally occurring PCV2 exposure, i.e., field studies. NB: This is a change from the prior review where group-level allocated studies were excluded. In addition to the PICOD criteria described above, eligibility criteria will include a full text in English with more than 500 words. Both published and non-published studies are eligible, provided they report a primary research study with a concurrent comparison group using an eligible study design.
Information sources	9	The search will be conducted using the MSU Web of Science license (CAB abstracts® and Medline®). Additional sources will be the reference lists of relevant manuscripts and the conference proceedings for the Annual Meeting of the American Association of Swine Veterinarians (AASV), the Allen Leman Swine Conference, the Iowa State University Swine Disease Conference for Swine Practitioners, and the International Pig Veterinary

Society (IPVS) Congress will be searched within the Swine Information Library(http://www.aasv.org/library/swineinfo/) from 2006 to the day of the search.

Search strategy 10 The search terms for the electronic databases will be a combination of terms that capture the population and the intervention combined with AND terms. This search is unchanged from the prior review. The proposed search strategy for Medline® is provided in Table *1*. The proposed search for CABI is in Table 2.

Table 1: Medline® search strings

Population	Intervention
(Barrow OR Barrows OR Boar OR Boars OR Feeder OR Finishing OR Gilt OR Gilts OR Hog OR Hogs OR Pig OR Piglet OR Piglets OR Pigs OR Porcine OR Shoats OR Sow OR Sows OR Swine)	Med

Table 2: *CABI*® search strings

Population	Intervention
(Barrow OR Barrows OR Boar OR Boars OR Feeder OR Finishing OR Gilt OR Gilts OR Hog OR Hogs OR Pig OR Piglet OR Piglets OR Pigs OR Porcine OR Shoats OR Sow OR Sows OR Swine)	TS=(Circoviridae OR Circovirus OR PCV-2 OR pcv2d OR PCVD "Porcine circovirus" OR "Porcir "Porcine circovirus associated d circovirus disease" OR "Porcine "Porcine circovirus-2" OR "Porc disease complex" OR "Postwear wasting disorder" OR "Porcine F Multisystemic Wasting Syndrom AND (Immunisation OR Immun OR Immunity OR Immunizatior Immunized OR Immunoprophy OR Interventions OR Vaccinate Vaccination OR Vaccinations C Vaccines).

The AASV Swine Information Library allows Boolean search terms but does not have an export function, requiring manual searching citations. Therefore, the search in AASV SIL will use the intervention and the outcome because the population is already implied in the information

		source : PCV* AND (vaccin*) AND (dead* OR mortality OR gain) -1000 records limited to SIL.
Study records:		
Data management	11a	Citations identified will be uploaded into the reference management software in DistillerSR® (Evidence Partners, Ottawa), and duplicates with more than 90% match will be manually reviewed for exclusion.
Selection process	11b	2 levels of screening will be used to identify relevant studies. The title/abstract form screening question will be • "Does the citation appear to describe an assessment of a commercially available PCV2 vaccine with a natural exposure to PCV2 in an intensive swine production system?" We will search for citations included in the prior review and screen these for inclusion to train the AI tool. We will use the built-in machine-assisted citation prioritization in DistillerSR®. This citation prioritization allows citations to be automatically reordered such that more likely relevant references are presented to the reviewer sooner, which allows the collection of full texts and full-text screening to begin sooner. After screening 500 prioritized citations, we will use the AI tool as the reviewer. We will use the following questions at the second level of screening based on the full text. • Does the study report in English and more than 500 words? • Does the study describe an assessment of one of the commercially available PCV2 vaccines within a field trial with natural exposure to PCV2? • Does the study report both the vaccine and its administration in accordance with the manufacturer's specifications? • Does the study report average daily gain and or mortality from wean to finish? • Is the PRRSV status of the herd reported? For AASV swine information library, screening on title and abstract will happen on the webpage, and citations considered relevant will be added to the 2nd level of screening.
Data collection process	11c	Forms for eligibility screening, data extraction, and risk of bias will be created in DistillerSR®. Two reviewers working will independently conduct each step. Pre-testing of forms is not required as we are updating the prior review.
Data items	12	The data items extracted will be (1) trial characteristics, (2) intervention, (3) outcome data, and (4) risk of bias.

		Trial population characteristics The extracted information about the trial population included the number of animals enrolled, the country of study, the PRRSV status, funded source **Interventions** The extracted information about the interventions included the PCV-II vaccine used – commercial name) and the type of control group (saline, no product, adjuvant only, other vaccines). We did not extract the vaccination regime as this was defined in the eligibility criteria, i.e., manufacturer's recommendations for piglets.
Outcomes and prioritization	13	The outcome of interest was ADG (g/day) from weaning (approximately three to six weeks of age) to late finishing prior to slaughter (approximately 23–28 weeks of age) for each trial arm. Other ADG periods will not be extracted. Other outcome data extracted were treatment-group level measures of variation i.e., SD, standard error of the mean (SEM). When studies reported results by subgroups (such as sex, genetic designation), the subgroup level data were extracted if each mean and SEM could be obtained using the method above. For mortality, we will extract the adjusted estimate of the odds ratio if available, if studies not available, we will extract the unadjusted odds ratio and finally the raw darm-level data without adjustment.
Risk of bias in individual studies	14	We will use a modified risk-of-bias tool for randomized trials based on the Cochrane ROB 2 tool but places less emphasis on allocation concealment. The Cochrane ROB-2 indicates that all studies that do not conceal allocation are at high risk of bias. The change will be that failure to report allocation concealment will follow the “yes/probably yes” path. Therefore the next question will be “was allocation random." Only studies that provide a complete decision of the random sequence generation and report no meaningful differences in baseline differences will be eligible of low risk of bias judgment. Studies that fail to report the allocation method and the baseline information will be at high risk of bias. All other studies will have an unclear risk of bias.
Data synthesis	15a	Data analysis will occur if we can extract at least one more study with data compared to the prior review.
	15b	The extracted outcome data for systematic review will be combined with the estimate from the clinical trial and synthesized using random effects network meta-analysis. A Bayesian hierarchical network meta-analysis, previously published, will be used to obtain the estimates of comparative efficacy for gain and mortality [2-5]. The arrangement of data and all the R scripts, JAGS scripts and BUGS required for the analysis of the data are available online at GitHub (https://github.com/a-oconnor/NETWORK_MA_FRONTIERS_TUTORIAL).

	15c	No additional analysis are anticipated, however ranking and pairwise probability of superiority would be required if the study goes for peer-review publication
	15d	We do not anticipate that network meta-analysis will not be feasible. The major issue will be failure of authors to report measures of variation for gain.
Meta-bias(es)	16	We will not conduct an analysis for small studies effects for pairwise comparison as this approach is not available for network meta-analysis . Such an approach would be needed for publication if that step is taken.
Confidence in cumulative evidence	17	We will not conduct a GRADE analysis, rather we will summarize the comparative estimate.
Report	18	The delivered report will include 1) The protocol provided here 2) Any protocol deviations 3) PRISMA flow chart 4) A tabular exclusion report for papers that have full text screening (Table 2 Da Silva et al 2014) 5) A tabular summary of characteristics of included studies (combined Table 3 and 4 Da Silva et al 5) The tabular results of all possible pairwise comparisons for mortality and average daily gain i.e., the risk ratio and mean difference. (Table 5, Da Silva et al 2014)

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

1. da Silva N, Carriquiry A, O'Neill K, Opriessnig T, O'Connor AM: **Mixed treatment comparison meta-analysis of porcine circovirus type 2 (PCV2) vaccines used in piglets**. *PREVENTIVE VETERINARY MEDICINE* 2014, **117**(3-4):413-424.
2. Hu D, O'Connor AM, Wang C, Sargeant JM, Winder CB: **How to Conduct a Bayesian Network Meta-Analysis**. *FRONTIERS IN VETERINARY SCIENCE* 2020, **7**.
3. Hu D, O'Connor AM, Winder CB, Sargeant JM, Wang C: **How to read and interpret the results of a Bayesian network meta-analysis: a short tutorial**. *ANIMAL HEALTH RESEARCH REVIEWS* 2019, **20**(2):106-115.
4. O'Connor AM, Hu D, Totton SC, Scott N, Winder CB, Wang B, Wang C, Glanville J, Wood H, White B *et al*: **A systematic review and network meta-analysis of bacterial and viral vaccines, administered at or near arrival at the feedlot, for control of bovine respiratory disease in beef cattle**. *ANIMAL HEALTH RESEARCH REVIEWS* 2019, **20**(2):143-162.

5. O'Connor AM, Totton SC, Shane D: **A systematic review and network meta-analysis of injectable antibiotic treatment options for naturally occurring swine respiratory disease**. *JOURNAL OF SWINE HEALTH AND PRODUCTION* 2019, **27**(3):133-149.

PRISMA flow chart for systematic reviews
CABI search – 1909 – all dates
Medline search 714 – 2005 onwards
380 duplicates automatically detected